

Remarks

Claims 32-84 are currently pending. Claim 56 has been amended to correct spelling or grammatical errors. Claims 50-54 have been amended to remove recitation of “contunious production.” Applicants believe that these amendments do not constitute new matter or raise new issues. Accordingly, Applicants respectfully request that the amendments be entered and receive full consideration.

Claim Objections

Claim 56 is objected to for allegedly containing grammatical or spelling errors. Applicants have amended Claim 56 to correct the alleged informalities. Applicants believe these objections to be moot in light of the amendments to Claim 56 and respectfully request the withdrawal of the objection.

35 U.S.C. 112, first paragraph

Claim 32 is rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner contends that written description is not present for “(c) adding one or more target substrates to the mixed culture in the bioreactor during the course of the culture.” Applicants respectfully traverse the rejection.

Applicants respectfully remind the Examiner that the standard for written description is conveyance of the claimed subject matter “with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath Inc. v Mahurka* 935 F2d 1555 -64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicants respectfully submit that support for part c of Claim 32 can be found throughout the specification and at least in the first paragraph on page 9 of the specification. Specifically, Applicants state that “the process step may also be performed successively in time by the sequential use if singular or plural target substance and/or substrates” (emphasis added). This directly and unambiguously includes the possibility that the target substrate is also added “during the course of the process” This statement of the specification clearly refers to the variant of the claimed method that the entire method is split into numerous individual process steps (see for instance p. 8, last paragraph). Consequently, the specification gives support for step (c) of claim 32, which limits the claimed method to a step-wise variant. Given the express support for feature c in the

specification, Applicants believe this rejection to be overcome and respectfully request its withdrawal.

35 U.S.C. 112, second paragraph

Claims 32-84 and 50-54 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite. In particular, the Examiner alleges that the recitation “wherein the continuously produced enzyme/substrate/fungus mixtures” in Claims 50-54 lacks antecedent basis and the recitation “of specific induction and inhibition” is “confusing and indefinite.” Applicants respectfully traverse this rejection.

Regarding the rejection of Claims 32-84, Applicants respectfully submit that the phrase “specific reduction and inhibition” is clear. Step (b) specifies parameters for the adjustment of a suitable selection pressure, namely physical/chemical parameters like moisture, pH, etc. Then follow further measure for adjusting selective conditions that are linked with an “and” relationship (i.e. mandatory), notably the specific induction via target substance or growth substrates (inducer substrates) or a combination thereof. Alternatively (linked with an “or” relationship) specific blocking (inhibiting) with “appropriate” specific inhibitors for installing a selection pressure are named. Both measures, the specific induction and the specific inhibition do not exclude each other as they can be directed to different marker organism or to different enzyme formation in the mixed culture. Thus, it can be desirable to enhance a distinct fungus species or enzyme formation and concomitantly to inhibit another fungus species or enzyme formation. This is reflected by the wording “or a combination of specific induction and inhibition.” Additionally, Applicants respectfully point out that the original claims both statements were linked with an “and/or” relationship. Applicants submit that as presently amended, the claims are clear as evidenced here and respectfully request that the rejection be withdrawn.

Regarding claims 50-54, the Examiner alleges that the phrase “continuously produced enzyme/substrate/fungus mixtures” is without antecedent basis. Claims 50-54 have been amended herein to remove recitation to continuous production of the mixtures. Applicants respectfully point out that, as amended, the claims are drawn to a method of producing an enzyme by contacting microorganisms with target substrates. Thus, the bioreactor culture is necessarily a mixture of the microorganism, the substrate, and the product of the microorganism

and its contact with the substrate i.e., the enzyme. Applicants believe this rejection to be moot in light of the amendments to Claims 50-54 and respectfully request its withdrawal.

35 U.S.C. 103

1. Claims 32-38, 41-45, 49-56, 71-73, and 83 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. (1999) *Bioresource Technology* 68: 173-178 in view of Pandey A. (2003) *Biochemical Engineering Journal* 13: 81-84 in view of Tenerdy et al. (2003) *Biochemical Engineering Journal* 13: 169-179. Applicants respectfully traverse this rejection.

In the recent *KSR Int'l Co. v Teleflex, Inc.* ruling, the Supreme Court has reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. 103(a). *KSR Int'l Co. v. Teleflex, Inc. (KSR)*, No 04-1350 (U.S. Apr. 30, 2007). The three factual inquiries under *Graham* require examination of: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere (Graham)*, 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). Additionally, the court in *Graham* noted a fourth consideration for the determination of obviousness would be any objective evidence of secondary considerations such as unexpected results, unmet need in the art, and commercial success.

Furthermore, in order to establish a prima facie case of obviousness, the examiner has the initial burden of supporting the conclusion of non-obviousness. In particular, the Examiner has the initial burden of ascertaining the differences between the claims and the prior art which requires interpreting both the art and the claims as a whole. Put another way, "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). Applicants respectfully point out that as presently amended, this burden has not been met. In particular, the Examiner has not shown it would be obvious to "add one or more target substrates to the mixed culture in the bioreactor during the course of the culture."

As the Examiner is aware, Claim 32 was previously amended to recite a semisterile culture method for producing a defined enzyme mixture, metabolite mixture, or combination thereof comprising amongst other things, "(c) adding one or more target substrates to the mixed culture in the bioreactor during the course of the culture." Applicants respectfully point out that

this feature is not taught or suggested by any of the cited references. Moreover, the combination of the cited references fails to teach or suggest this limitation.

Furthermore, Applicants respectfully submit that despite assertions to the contrary, it would not be obvious and there would be no motivation for a person skilled in the art to add the target substrate during the course of cultivation and that this action would be justified with the alleged consumption of the target substrate during the course of the reaction especially of a continuous process. Applicants respectfully remind the Examiner that The Court has further recognized that the requirement for a teaching, suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, which was established by the Court of Customs and Patent Appeals, provides a helpful insight for determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). The Examiner asserts on page 3 of the present action “that the *KSR* decision forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness.” Applicants respectfully point out that while the Court stated that the TSM rationale was not the only test, it was still a valid and insightful means to determine obviousness and though not the exclusive test, TSM was still a valid test. Despite removing the rigid application of TSM from the determination of obviousness, the Court maintained that any analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it is “important to identify reasons that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements” in the manner claimed, because “inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR* at 14, 15.

Further, courts have generally recognized that a showing of a prima facie case of obviousness necessitates three requirements: (i) some suggestion or motivation, either in the references themselves or in the knowledge of a person of ordinary skill in art, to modify the reference or combine the references’ teachings; (ii) a reasonable expectation of success; and (iii) the prior art references must teach or suggest all of the claim limitations. See e.g., *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999); *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996).

Applicants would like to emphasize that they are not arguing for a rigid application of the teaching-suggestion-motivation (TSM) rationale, which requires that a printed statement be present for a finding of obviousness. Instead, Applicants submit that the Supreme Court acknowledged that the TSM test was one of a number of valid rationales that could be used to determine obviousness. *KSR* at 1727 (2007); see *MPEP* 2141; *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006). Applicants respectfully submit that the addition of the target substrate during the course of the cultivation (according to step (c) of claim 32) is not intended in order to compensate for the consumption of target substrate, but only serves the purpose of an enzyme induction. Notably, this repetitious additions serve the purpose of the optimization of the quality of the enzyme spectrum as the target substrate in the process after inoculation, i.e. during the course of the inoculation. This reasoning behind the addition is not readily apparent for the person skilled in the art in the area of solid fermentation. In fact a person skilled in the art would not contemplate the repetitious addition of the target substrate for that purpose nor would he be aware of the advantage connected therewith, namely that by the addition of the target substrate during the course of the addition process the established stable and biomass mixed culture, which has been established so far, is now further conditioned in the direction of the target substrate, which has consequences for further enzyme formation. This is reflected in the specification for instance on p. 9, l. 4 and p. 10, paragraph 1. Accordingly, the person skilled in the art would thus have no motivation to add further target substrate during the course of the addition process.

The practical aspect of this sequential process is reflected in the selection of the type of the bioreactors, especially the preferred screw bioreactor as shown in Fig. 1 of the application, which is - due to the incomplete or missing remixturing of a subsequently added target substrate - particularly suitable for the adaption procedure. Thus, applicant believes that the subsequent addition of target substrate is not rendered obvious by any of the cited references. Therefore, as amended, the recited art alone or in combination fails to teach or suggest all the limitations of the claims, and the combination of cited references additionally fails to provide the required motivation to arrive at Applicants' invention. Thus, the cited art, alone or in combination fails to make the present claims obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

2. Claims 32, 74-77, and 84 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Tengerdy et al. and in further view of WO 02/10099. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

3. Claims 32-45 and 78-80 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Tengerdy et al. and in further view of Raimbault, M. 1998) Elec. Journal. of Biotech. 1: 174-188. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

4. Claims 32-38, 41-48, and 57 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Bradley et al. (U.S. Patent No. 6,485,952) and in further view of Pandey et al. (2000) Process Biochemistry 53: 1153-1169. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

5. Claims 32-38, and 58-62 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of De Vries et al. (1997) *Applied and Environmental Micro.* 63: 4638-4644; and O-Toole (1999) *J. Agric. Food Chem.* 47: 363-371 and of El-batal (2001) *Food Reseach International* 34: 715-720. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

6. Claims 32-38, and 63-66 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Malherbe et al. (2002) Review in Environmental Science and BioTechnology 1: 105-225 and De Vries and O'Toole and El-batal. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

7. Claims 32-38, and 67-70 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Tengerdy et al. and of Chiou et al. (2002) Asian-australaasian journal of animal science and in further view of De Vries and O'Toole and El-batal. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

8. Claims 32-38 and 81-83 are rejected under 35 U.S.C. 103 as allegedly being obvious over Gutierrez-Correa et al. in view of Pandey A. et al. and in further view of Palit et al. (2001) Brazillian Archives of Biology and Technology 44: 107-111 and Pandey A. et al. (1999) Current Science 77: 149-162. Applicants respectfully traverse this rejection.

As noted above, the cited combination fails to teach all the features of the present claims or provide motivation to make the necessary changes and combinations to arrive at the present invention in Claim 32. Because Claim 32 is not obvious, claims dependent thereon are not

obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

An EFS web payment in the amount of \$960.00, representing \$550.00 the fee for a small entity under 37 C.F.R. § 1.17(a)(3) for a three (3) Extension of Time and \$405, the fee for a small entity under 37 C.F.R. § 1.17(e) for a Request for Continued Examination; a Request for Continued Examination; and a Request for a three (3) month Extension of Time are being submitted electronically. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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May 19, 2011
Date